Kidney International, Vol. 38 (1990), pp. 948–955

Renal function in obstructive jaundice in man: Cholangiocarcinoma model

VISITH SITPRIJA, UDOMPORN KASHEMSANT, AMNACH SRIRATANABAN, SILLAWAT ARTHACHINTA, and VICHAI POSHYACHINDA

Departments of Medicine and Radiology, Chulalongkorn University Hospital, Bangkok, Thailand

Renal function in obstructive jaundice in man: Cholangiocarcinoma model. Renal function with respect to water clearance and renal hemodynamics was studied in 15 patients with obstructive jaundice due to cholangiocarcinoma. The results were compared with those of the control normal subjects. There was no change in renal function in the patients with mild to moderate jaundice, with total serum bilirubin from 8.0 to 15.1 mg/dl. Increased urinary sodium excretion and decreased free water and negative water clearances were observed in the patients with severe jaundice with total serum bilirubin from 27.0 to 40.4 mg/dl and normal serum albumin. Renal blood flow was normal, but creatinine clearance was decreased. In severely jaundiced patients with serum bilirubin from 30.5 to 40.1 mg/dl and hypoalbuminemia urinary sodium excretion, free water clearance, negative water clearance, renal blood flow and creatinine clearance were decreased. There was salt and water retention in this group. The findings suggest that in severe jaundice there is inhibition of sodium chloride reabsorption in the thick ascending limb of Henle's loop. ADH and increased hydraulic conductivity of the collecting tubules possibly contribute to decreased free water clearance. In severely jaundiced patients with hypoalbuminemia this salt losing effect is converted to salt retention by increased proximal tubular reabsorption of sodium.

Renal function in obstructive jaundice has been the subject of great interest ever since the association between jaundice and renal failure was described [1, 2]. Renal hemodynamic study has shown both decreased [3–5] and normal renal blood flow [6–8]. Urinary dilution capacity has been shown to be impaired in obstructive jaundice due to common bile duct ligation attributed to increased proximal tubular reabsorption of sodium [9, 10], lack of renal vasodilatation [11] during volume expansion and increased antidiuretic hormone activity [12]. These results were based mainly on animal studies using common bile duct ligation model, and the degree of jaundice was in most cases mild. In contrast, hyponatremia with natriuresis has been observed in a patient with severe jaundice due to carcinoma of common bile duct [13]. In our preliminary study in patients with severe obstructive jaundice the renal ability to conserve sodium during sodium restriction was found to be impaired [14]. Furthermore exaggerated natriuresis in response to volume expansion has been shown in the patients with primary biliary cirrhosis [15]. The results are therefore at variance with the reports in animals. The discrepancy in results could reflect the difference in studied subjects or models and the degree of jaundice. The data in man are in fact very scanty, and may not be identical to those of animals. The high incidence of cholangiocarcinoma due to opisthorchiasis [16] with obstructive jaundice in Thailand has provided the opportunity to study the effects of jaundice in renal function in man. It is therefore the purpose of this investigation of study the renal function in the patients with varying degrees of jaundice due to biliary obstruction secondary to cholangiocarcinoma.

Received for publication November 8, 1989
and in revised form April 20, 1990
Accepted for publication May 30, 1990

Methods

Fifteen patients with obstructive jaundice due to cholangiocarcinoma, ranging in age from 36 to 50 years, were studied. The diagnosis in all cases was confirmed by histopathologic study of the tumor tissue obtained at surgery, and no gross evidence of cirrhosis of the liver was seen during surgery. All had Opisthorchis viverrini infection diagnosed by stool examination. Eleven were male and four were female. The clinical data are shown in Table 1. The total serum bilirubin varied from 8.0 to 40.4 mg/dl. The serum creatinine ranged from 0.9 to 1.4 mg/dl, and urinalysis was normal. There was no clinical evidence of renal disease or cardiac disease. Neither was there evidence of intravascular hemolysis as assessed by the hemoglobin level, serum haptoglobin and reticulocyte count. The patients were afebrile with the mean arterial pressure ranging from 78 to 97.3 mm Hg. The duration of illness varied from two to seven weeks averaging five weeks. Those with severe jaundice had longer duration of illness. The patients were classified into three groups based on the level of serum bilirubin and serum albumin.

Group 1. Five patients in this group had the total serum bilirubin ranging from 8.0 to 15.1 mg/dl. The serum albumin ranged from 3.3 to 4.0 g/dl.

Group 2. In this group of five patients the total serum bilirubin varied from 27.0 to 40.4 g/dl, and serum albumin ranged from 3.5 to 3.9 g/dl.

Group 3. There were five patients in this group with the total serum bilirubin ranging from 30.5 to 40.1 mg/dl. The serum albumin was decreased, and varied from 2.4 to 3.0 g/dl.

Of interest is the finding that the mean arterial pressure in group 2 and 3 patients was significantly lower than that in group 1 patients. The patients in group 3 had lowest mean arterial

Table 1. Clinical data

Patient	Age	Sex	Duration of jaundice *weeks*	MAP	BT/BD *mg/dl*	AP *IU*	S_{GOT}	S_{GPT}	S_{Alb}	BUN	S_{Cr}
							σ U		*g/dl*	*mg/dl*	
Group 1											
1	40	F	2	94.0	8.0/2.7	102	41	41	3.3	12	1.1
2	42	M	2	94.0	9.2/3.9	120	62	52	3.6	10	0.9
3	37	M	3	90.0	12.4/4.2	140	92	80	4.0	14	1.2
4	50	M	3	95.3	15.1/4.8	142	84	68	3.9	10	1.2
5	46	M	2	97.3	10.4/3.9	127	100	84	3.9	16	1.0
Mean ± SD	43 ± 5		2.4 ± 0.5	94.1 ± 2.7	11 ± 2.8/ 3.9 ± 0.8	126.2 ± 16.3	75.8 ± 24.1	65 ± 18.3	3.7 ± 0.3	12.4 ± 2.6	1.1 ± 0.1
Group 2											
6	40	F	5	94.0	30.2/14.1	141	165	112	3.9	15	1.2
7	39	M	6	92.9	35.1/15.2	155	112	87	3.5	17	1.3
8	45	M	7	88.0	40.4/16.0	162	170	121	3.6	14	1.1
9	42	M	5	83.3	32.4/13.7	157	124	104	3.8	11	1.0
10	39	M	5	84.7	27.0/12.2	146	144	99	3.9	12	1.1
Mean ± SD	41.0 ± 2.5		5.6 ± 0.9	88.5 ± 4.7[a]	33.0 ± 5.1/ 14.3 ± 1.5	152.2 ± 8.5	143.0 ± 25.2	104.6 ± 12.9	3.7 ± 0.2	13.8 ± 2.4	1.1 ± 0.1
Group 3											
11	47	F	5	90.0	30.6/10.8	125	126	102	2.6	13	1.2
12	36	M	5	84.7	30.5/11.4	122	170	105	2.8	16	1.3
13	38	F	6	86.7	38.4/15.5	170	154	120	3.0	20	1.4
14	49	M	6	78.0	32.6/12.6	147	172	95	2.5	19	1.4
15	41	M	7	80.0	40.1/17.3	205	175	97	2.4	18	1.4
Mean ± SD	42.2 ± 5.6		5.8 ± 0.8	83.9 ± 4.9[b]	34.4 ± 4.5/ 13.5 ± 2.8	153.8 ± 34.5	159.4 ± 20.4	103.8 ± 9.9	2.7 ± 0.2	17.2 ± 2.8	1.3 ± 0.1

Abbreviations are: BT, total bilirubin; BD, direct bilirubin; AP, alkaline phosphatase; S_{GOT}, serum glutamic oxaloacetic transaminase; S_{GPT}, serum glutamic pyruvic transaminase; S_{Alb}, serum albumin; S_{Cr}, serum creatinine; BUN, blood urea nitrogen; MAP, mean arterial pressure on admission.

[a] $P < 0.05$; [b] $P < 0.0001$ when compared with group 1

pressure (Table 1). Presacral edema was present in all patients in this group.

Five normal subjects without jaundice with normal serum creatinine and negative urinalysis served as control. Although it would be more ideal to compare these patients with comparable ill hospitalized patients without jaundice this is not feasible in practice. The mean arterial pressure in the subjects in this control group did not differ from those patients in group 1.

All patients including normal subjects were placed on the hospital diet with 40 g of protein and 120 mEq of sodium. Complete food consumption was assured in all. The project was approved by the ethical committee of the hospital, and the study was performed before the operation after informed consent from all patients and subjects.

Renal blood flow

Renal blood flow was measured in three patients of each group on the second hospital day. A total of 1.5 to 2.0 mCi of 133 Xe (Radiochemical Centre, Amersham, UK, Code No. XAS. 1P) diluted with normal saline solution to 2.3 ml was selectively injected into the renal artery through transfemoral catheterization. The radioactivity was recorded for 45 minutes by a ratemeter and linear recorder with spectrometer set at 50 to 200 keV. The blood flow was computed according to the method of Thorburn et al [17].

Clearance study

Water diuresis. On the third hospital day an oral load of water (20 ml/kg) was given within 20 to 30 minutes, and the urine was collected every 30 minutes. After each urine collection water was orally given in an amount equal to the urine volume. The study period was three hours. Blood was sampled at the midpoint of each urine collection.

Hydropenia, pitressin and mannitol diuresis. Food and fluids were omitted for 14 hours before the study was performed on the fourth hospital day. Each patient was given 10% mannitol in half strength normal saline with aqueous pitressin (50 mU/kg/hr) at the rate of 10 ml/min for a period of two hours. Urine was collected every 30 minutes, and blood was obtained at the midpoint of each urine collection.

The clearance study was repeated two weeks later in three patients of group 2 (patients 7, 9 and 10) after jaundice was decreased by biliary decompression. Their total serum bilirubin was 1.2, 1.0 and 1.0 mg/dl, respectively.

Determinations were made in plasma and urine of creatinine [18], sodium (Beckman flame photometer) and osmolality (Advanced Instruments Osmometer Model 3W). Because of bilirubin interference of creatinine determination the end-point Jaffe method was used for creatinine analysis [19].

Creatinine clearance (C_{Cr}), osmolal clearance (C_{Osm}), free water clearance (C_{H_2O}), negative water clearance (Tc_{H_2O}), and sodium clearance (C_{Na}) were calculated.

Table 2. Renal blood flow

Patient	Renal blood flow *ml/100 g/min*				
	Component				
	I	II	III	IV	Total
Group 1					
1	425	91	24	21	561
3	406	109	22	18	555
5	400	100	22	17	539
Mean ± SD	410 ± 13	100 ± 9	22.6 ± 1.2	18.7 ± 2.1	551.7 ± 11.4
Group 2					
6	420	99	19	16	554
8	390	105	20	14	529
9	411	102	24	18	555
Mean ± SD	407 ± 15.4	102 ± 3	21 ± 2.6	16 ± 2	546 ± 14.7
Group 3					
12	210	52	20	20	302
13	204	43	23	18	288
14	212	45	26	19	302
Mean ± SD	208.7 ± 4.2[c]	46.7 ± 4.7[a]	23 ± 3	19 ± 1	297.3 ± 8.1[b]
Normal subjects ($N = 5$)					
Mean ± SD	414 ± 12	104 ± 9.3	24.2 ± 4.3	16.9 ± 6.0	559.1 ± 29.2

[a] $P < 0.01$; [b] $P < 0.001$; [c] $P < 0.0001$ when compared with normal

The data in each group were compared with those of the control patients using the unpaired *t*-test [20].

Results

Renal blood flow

The results of renal blood flow study are shown in Table 2, and are compared with renal blood flow in normal subjects from the previous study [21].

Group 1. The total renal blood flow ranged from 539 to 561 ml/100 g/min with the mean of 551.7 ml/100 g/min. The flow in each component was comparable to that of the normal subjects.

Group 2. The total renal blood flow varied from 529 to 555 ml/100 g/min averaging 546 ml/100 g/min. The flow in each component was within the normal range.

Group 3. The total renal blood flow was decreased, and ranged from 288 to 302 ml/100 g/min. The flow in components I and II was markedly decreased from the normal values.

Clearance data

Water diuresis. The results are shown in Table 3. In the control group the maximal urine volume ($\dot{V}$) ranged from 10.4 to 12.9 ml/min. Urine osmolality (U_{Osm}) at the maximal urine flow varied from 50 to 58 mOsm/kg. C_{Osm} ranged between 1.9 and 2.8 ml/min, giving C_{H_2O} values from 8.5 to 10.1 ml/min. The mean C_{Cr} was 126.4 ml/min. C_{Na} ranged from 0.9 to 1.2 ml/min.

In Group 1 $\dot{V}$ ranged from 10.2 to 12.7 ml/min. U_{Osm}, C_{Osm}, C_{H_2O}, C_{Na}, and C_{Cr} did not differ from those of the control group when statistically analyzed (Table 3).

In Group 2 $\dot{V}$ ranged from 7.0 to 8.4 ml/min (Table 3). U_{Osm}, C_{Osm}, U_{Na}, and C_{Na} were significantly higher than those of the control patients. C_{H_2O} was significantly lower than the control ($P < 0.01$). C_{Cr} averaged 79.6 ml/min, significantly less than the control group.

In Group 3 $\dot{V}$ ranged from 4.1 to 5.2 ml/min. U_{Osm} varied from 90 to 116 mOsm/kg. Significant decreases in C_{Osm}, C_{H_2O}, U_{Na}, C_{Na}, and C_{Cr} were observed when compared with those of the control group.

When expressed per 100 ml of C_{Cr}, free water clearance was decreased in groups 2 and 3.

The repeat study in patients 7, 9 and 10 of group 2 when the serum bilirubin was normal showed normal free water clearance and creatinine clearance (Table 3).

Hydropenia, pitressin and mannitol diuresis

The results are shown in Table 4. In the control group the maximal urine flow ($\dot{V}$) ranged from 5.0 to 6.0 ml/min with U_{Osm} from 604 to 657 mOsm/kg and U_{Na} from 88 to 113 mEq/liter. C_{Osm} varied from 10.7 to 12.5 ml/min, giving negative water clearance (Tc_{H_2O}) between 5.6 and 7.1 ml/min. C_{Cr} ranged from 99 to 111 ml/min.

In Group 1 $\dot{V}$ ranged from 5.2 to 6.1 ml/min. U_{Osm} varied from 609 to 651 mOsm/kg. C_{Osm} ranged between 11.4 and 12.6 ml/min, and Tc_{H_2O} between 6.3 and 7.2 ml/min. U_{Na} ranged from 84 to 102 mEq and C_{Cr} from 98 to 108 ml/min. The results did not differ from those in the control group.

In Group 2 significant decreases from the control in U_{Osm}, C_{Osm}, C_{Cr} and Tc_{H_2O} were noted. U_{Na} was increased above the control averaging 134.4 mEq/liter (Table 4).

In Group 3 $\dot{V}$ varied from 4.2 to 4.8 ml/min. Significant decreases from the control group in U_{Osm}, C_{Osm}, Tc_{H_2O}, U_{Na}, and C_{Cr} were observed.

It might be argued that negative water clearance could be interfered by the previous water load. Yet, this was performed in all groups, and thus should be acceptable on the comparative basis. Negative water clearance, expressed per 100 ml of C_{Cr}, was decreased in groups 2 and 3. This returned to the control values when jaundice subsided (patients 7, 9 and 10) two weeks after biliary decompression.

Table 3. Effects of water diuresis

	V	U_{Osm}	C_{Osm}	C_{H_2O}	U_{Na}	C_{Na}	C_{Cr}	$C_{H_2O} \times 100/C_{Cr}$
	ml/min	*mOsm/kg*	*ml/min*		*mEq/liter*	*ml/min*		
Control								
Subject								
1	10.4	50	1.9	8.5	12	0.9	122	7.0
2	11.2	55	2.3	8.9	13	1.1	112	7.9
3	12.9	58	2.8	10.1	13	1.2	128	7.9
4	11.3	52	2.2	9.1	14	1.2	134	6.8
5	11.2	55	2.3	8.9	15	1.2	136	6.5
Mean ± SD	11.4 ± 0.9	54 ± 3.1	2.3 ± 0.3	9.1 ± 0.6	13.4 ± 1.1	1.1 ± 0.13	126.4 ± 9.7	7.2 ± 0.6
Group 1								
Patient								
1	11.2	52	2.2	9.0	14	1.2	104	8.7
2	12.7	55	2.6	10.1	15	1.4	134	7.5
3	10.8	60	2.4	8.4	13	1.1	131	6.4
4	11.2	56	2.3	8.9	13	1.1	129	6.9
5	10.2	58	2.2	8.0	16	1.2	128	6.3
Mean ± SD	11.2 ± 0.9	56.2 ± 3.0	2.3 ± 0.2	8.9 ± 0.8	14.2 ± 1.3	1.2 ± 0.1	125.2 ± 12.1	7.2 ± 0.9
Group 2								
6	8.4	160	4.8	3.6	57	3.6	86	4.2
7	8.0	172	4.9	3.1	49	2.9	71	4.4
8	7.0	150	3.8	3.2	69	3.6	84	3.8
9	7.5	162	4.4	3.1	50	2.8	75	4.1
10	7.9	162	4.6	3.3	61	3.6	82	4.4
Mean ± SD	7.8 ± 0.5[a]	161.2 ± 7.8[d]	4.5 ± 0.4[a]	3.3 ± 0.2[c]	57.2 ± 8.3[b]	3.3 ± 0.4[b]	79.6 ± 6.3[a]	4.2 ± 0.2[b]
7[c]	10.8	58	2.3	8.5	12	1.0	120	7.1
9[e]	11.2	60	2.4	8.8	10	0.9	118	7.5
10[e]	12.1	57	2.5	9.6	13	1.2	129	7.4
Mean ± SD	11.4 ± 0.7	58.3 ± 1.5	2.4 ± 0.1	9.0 ± 0.6	11.7 ± 1.5	1.0 ± 0.2	122.3 ± 5.9	7.3 ± 0.2
Group 3								
11	4.8	96	1.6	3.2	8	0.3	60	5.3
12	5.2	90	1.6	3.6	10	0.4	70	5.1
13	4.1	102	1.5	2.6	9	0.3	62	4.2
14	4.0	112	1.6	2.4	8	0.2	63	3.8
15	4.2	116	1.7	2.5	10	0.3	66	3.8
Mean ± SD	4.5 ± 0.5[b]	103.2 ± 10.8[b]	1.6 ± 0.07[a]	2.9 ± 0.5[c]	9.0 ± 1.0[a]	0.3 ± 0.7[b]	64.2 ± 3.9[b]	4.4 ± 0.7[a]

[a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$; [d] $P < 0.0001$ when compared with control
[e] Repeat determination when jaundice was decreased

Discussion

Our study is interesting in that the patients in groups 2 and 3 had severe jaundice with the serum bilirubin at the supraphysiologic concentration. The serum bilirubin exceeded 26 mg/dl. It has been suggested that in man at the serum bilirubin of 25 to 30 mg/dl bilirubin excretion in the urine approximates the hepatic production of conjugated bilirubin of 250 mg/day, and the serum bilirubin usually does not exceed this level [22]. The higher value would indicate hemolysis or impaired renal function. In our patients the serum bilirubin exceeded 26 mg/dl. There was no clinical evidence of hemolysis, but there was some reduction in creatinine clearance. It cannot be excluded that there was selective impaired tubular secretion of bilirubin since bilirubin can be transported through tubular secretion [23]. It should be pointed out that these patients were admitted to the hospital late in the course of the disease. They sought medical advice five to seven weeks of the illness which would be unusual in the western countries. The model can thus be regarded as an experiment with nature providing a unique opportunity to study the effects of severe jaundice in man.

Admittedly, there is paucity of data in patients with total bilirubin level ranging from 16 to 26 mg/dl in this study. Nevertheless several findings were revealed from this study. There was no change in renal function with respect to renal hemodynamics and water clearance in the patients with mild to moderate degree of obstructive jaundice. In the patients with severe jaundice with total serum bilirubin above 26 mg/dl generation of free water and negative water clearance was impaired. Yet, the renal blood flow was normal except for group 3 with hypoalbuminemia in which there was reduction in the renal blood flow especially the cortical flow. Creatinine clearance was decreased in both groups 2 and 3 with severe jaundice. Although creatinine clearance does not truly represent the glomerular filtration rate the data are valid in the comparative sense, and it is reasonable to state that glomerular filtration rate was decreased in severe jaundice.

In the previous hemodynamic studies in obstructive jaundice there were conflicting results in the renal blood flow. In baboons with common bile duct ligation the total renal blood flow was found to be decreased, and this was reversed by phentolamine but not by saralasin [4]. Renal denervation did not alter the renal blood flow, however [24]. Levy, Wexler and Fechner have shown in dogs with common bile duct ligation that renal vasoconstriction was mediated through renin-angiotensin activation [25]. Yet, in some reports the renal blood flow has been found to be normal [6–8]. It is felt that renal hemodynamics is the net result of effects of vasoconstrictors and vasodilators released. There is an increase in renal production

Table 4. Effects of hydropenia, mannitol diuresis and pitressin

	V	U_{Osm}	C_{Osm}	Tc_{H_2O}	U_{Na}	C_{Cr}	$Tc_{H_2O} \times 100/C_{Cr}$
	ml/min	*mOsm/kg*	*ml/min*		*mEq/liter*	*ml/min*	
Control							
Normal subject							
1	5.1	612	10.7	5.6	101	101	5.5
2	6.0	604	12.5	6.5	88	99	6.6
3	5.2	621	11.0	6.2	105	104	6.0
4	5.6	642	12.2	6.6	99	111	5.9
5	5.0	657	12.2	7.2	113	102	7.1
Mean ± SD	5.4 ± 0.4	627.2 ± 21.9	11.7 ± 0.8	6.4 ± 0.6	101.2 ± 9.1	103.4 ± 4.6	6.2 ± 0.6
Group 1							
Patient							
1	6.1	609	12.6	6.5	84	100	6.5
2	5.4	640	11.7	6.3	101	98	6.4
3	5.7	638	12.3	6.6	101	98	6.7
4	5.2	642	11.4	7.2	102	104	6.9
5	5.2	651	11.6	6.4	102	108	5.9
Mean ± SD	5.5 ± 0.4	636 ± 15.9	11.9 ± 0.5	6.6 ± 0.4	98 ± 7.8	101.6 ± 4.3	6.5 ± 0.4
Group 2							
6	4.2	484	7.0	2.8	126	62	4.5
7	5.1	514	8.9	3.8	132	83	4.6
8	4.5	500	7.7	3.2	145	74	4.3
9	4.7	495	7.9	3.2	133	79	4.1
10	5.6	490	9.4	3.8	136	84	4.5
Mean ± SD	4.8 ± 0.5	496.6 ± 11.4[b]	8.1 ± 0.9[a]	3.4 ± 0.4[a]	134.4 ± 6.9[a]	76.4 ± 8.9[a]	4.4 ± 0.2[a]
7[c]	5.5	631	11.9	6.4	91	112	5.7
9[c]	5.2	650	11.6	6.4	87	108	5.9
10[c]	5.1	644	11.2	6.1	96	98	6.2
Mean ± SD	5.3 ± 0.2	641.7 ± 9.7	11.8 ± 0.2	6.3 ± 0.2	91.3 ± 4.5	106 ± 7.2	5.9 ± 0.3
Group 3							
11	4.8	501	8.2	3.4	40	81	4.2
12	4.3	511	7.5	3.2	35	72	4.4
13	4.2	438	6.2	2.0	36	67	3.0
14	4.5	450	6.9	2.4	41	74	3.2
15	4.4	491	7.3	2.9	43	69	4.2
Mean ± SD	4.4 ± 0.2[a]	478.2 ± 14.4[b]	7.2 ± 0.7[a]	2.8 ± 0.6[a]	39 ± 3.4[b]	72.6 ± 5.4[b]	3.8 ± 0.6[a]

[a] $P < 0.05$; [b] $P < 0.01$ when compared with control
[c] Repeat determination when jaundice disappeared

PGE_2 in a study of Zambraski and Dunn with the net maintenance of renal blood flow [6]. Cioffi et al have demonstrated decreased vascular reactivity to catecholamines in obstructive jaundice [26]. Hypotension in obstructive jaundice has been attributed to PGE_2 with decreased peripheral vascular resistance. There is an exaggerated hypotensive response to volume depletion [27]. In this study the mean arterial pressure was significantly lower in the patients of groups 2 and 3 with severe jaundice than those in group 1 with milder degree of jaundice. In the patients who recovered the mean arterial pressure rose when the total serum bilirubin levels approached normal. In the previous study [14] hypovolemia was present in patients with severe obstructive jaundice. Group 3 patients with hypoalbuminemia had lower mean arterial pressure than group 2. Despite the low mean arterial pressure in group 2 patients the renal blood flow remained normal, indicating renal vasodilatation. This resulted in decreased creatinine clearance. The decreased renal blood flow and creatinine clearance in group 3 patients with low serum albumin could be due to hypovolemia secondary to reduced plasma oncotic pressure and the more decrease in mean arterial pressure. The release of vasoconstrictive mediators could be contributory.

It is well known that transport of sodium chloride through the ascending limb of Henle's loop and the medullary blood flow are important in the formation of free water and negative water clearance. Free water clearance is usually used as an estimate of the rate of sodium chloride reabsorption in the thick ascending limb on the condition that ADH release is suppressed. Without the suppression of ADH, which could be the case in this study, interpretation of the sum of C_{H_2O} and C_{Na} as the estimate of delivery of sodium to the distal nephron would be invalid, and thus will be ignored. In group 2 patients C_{Na} was increased while free and negative water clearances were decreased. Hemodynamic study in this group did not show alteration of renal blood flow in any component. The medullary blood flow was normal. Since sodium chloride transport through the thick ascending limb serves for both generation of free water and negative water clearances, impairment of formation of both free and negative water clearances and increased C_{Na} are therefore interpreted to indicate inhibition of sodium chloride reabsorption in the thick ascending limb [28]. Yet failure to suppress ADH release, which could account for decreased free water clearance, cannot be excluded, especially in the phase of decreased mean arterial pressure and presumed hypovolemia secondary to natriuresis. In addition, in a recent study it has been shown that bile salt increased hydraulic conductivity in cortical collecting tubules both at the basal and ADH stimulation, causing decreased water elimination [29]. In

group 3 patients the decrease in free water and negative water clearances was accompanied by decreased C_{Na}. The findings would suggest increased proximal tubular reabsorption of sodium. Hypoalbuminemia per se may decrease proximal tubular reabsorption of sodium due to diminished plasma oncotic pressure in the peritubular capillaries [30]. However, it is possible that hypoalbuminemia could reflect hepatic damage from prolonged biliary obstruction [31], and hepatic damage might be of sufficient degree to cause renal hemodynamic alteration either through decreased effective blood volume [32] or cardiac dysfunction [33], thus enhancing proximal tubular reabsorption of sodium. Hypoproteinemia itself can cause hypovolemia which could increase proximal tubular sodium reabsorption. The fact that the patients in this group had lower mean arterial pressure than the other groups supports the hemodynamic cause. Free water and negative water clearances were therefore decreased. The contributing role of aldosterone in decreasing sodium clearance cannot be excluded. The decreased free water clearance could also be attributed to the effect of ADH induced either by hypovolemia due to hypoalbuminemia or decreased effective blood volume. The ADH effect appeared to be pronounced in this group of patients evidenced by the presence of presacral edema. Unfortunately, the data on the plasma level of ADH are not available in this study.

The results of our study are therefore at variance with the experimental work in animals in which sodium retention was observed [9, 10]. This could reflect the difference in experimental subjects and the severity of jaundice. Our patients were unique in that they had very high serum bilirubin from prolonged biliary obstruction. In this study natriuresis was striking in severely jaundiced patients with normal serum albumin. However, it is not known at what level of serum bilirubin natriuresis and impaired water clearances started because of the lack of data in the patients with total serum bilirubin level ranging from 16 to 26 mg/dl. Although there were no data on 24-hour urine sodium, analysis of data from the previous study of 14 patients with obstructive jaundice, who had total serum bilirubin in a well distributed range of 6.2 to 49.2 mg/dl, has shown good positive correlation between the degree of jaundice and daily urine sodium excretion at the serum bilirubin over 20 mg/dl [14]. These patients had normal serum protein. On speculative basis it is plausible that renal function changes occur when the total serum bilirubin exceeds 20 mg/dl. However, the results in jaundiced patients with hypoalbuminemia agree with those reports in animals and in liver cirrhosis. In these patients the natriuretic effect of hyperbilirubinemia was overcome by increased proximal tubular reabsorption of sodium.

The mechanism responsible for inhibition of sodium chloride reabsorption in the ascending limb of Henle's loop is not known. From our data it appeared to be related to the degree of jaundice. Increased urinary sodium excretion was noted in the patients with serum bilirubin above 26 mg/dl and normal serum albumin. The duration of jaundice was at least five weeks. Yet this was reversible as shown in three patients (patients 7, 9 and 10) who had normal water clearance when jaundice subsided. It is not clear as to which factor in jaundice accounts for this function defect. In Gunn strain of rats bilirubin concentration was found to be several times higher in the renal medulla than in the cortex [34]. It has been postulated that a high concentration of unconjugated bilirubin in the renal medulla might interfere with sodium chloride transport through the ascending limb of Henle's loop. Deficiency in urinary concentration and dilution capacity in Gunn rats has been related to the presence of unconjugated bilirubin with its adverse effects on cellular function [35]. Attempts to decrease the serum bilirubin have been associated with improvement of renal function [35, 36]. In our study lowering of the serum bilirubin in patients 7, 9 and 10 without tumor resection was associated with the return of concentration and dilution capacity. Any humoral factor released by tumor capable of causing a defect in sodium reabsorption is therefore unlikely. Tubulointerstitial changes which might account for tubular dysfunction have not been observed in uncomplicated opisthorchiasis in our experience. The rapid reversibility of the renal defects following surgical correction of biliary obstruction in three patients suggests that renal structure remained reasonably intact despite prolonged and severe jaundice, and that renal changes were functional. In animal experiments cross circulation between jaundiced rats and normal rats has been shown to improve mitochondrial function and ATPase synthesis along with the decrease in jaundice [31].

Although one would expect the major contribution of conjugated bilirubin to the total serum bilirubin in obstructive jaundice, in practice both conjugated and unconjugated bilirubin are elevated [37]. In this study indirect bilirubin which reflects unconjugated bilirubin accounted for 60% of total bilirubin. This is quite common in severe obstructive jaundice in the tropics. It is thus possible that the elevation of unconjugated bilirubin might be high enough to cause impairment in generation of free water and negative water clearances as it does in the Gunn strain of rats. Unconjugated bilirubin decreases ATP content in the renal tubular cells and decreases para-aminohippurate uptake [38]. There is inhibition of oxidative phosphorylation in mitochondria with decreased ATPase activity [39]. The effects are similar to the ethacrynic acid [38]. Intracellular sodium is increased while intracellular potassium is decreased. In microperfusion study in rat, natriuresis could be induced by bile salt and this was believed to be due to inhibition of proximal tubular reabsorption of sodium [40]. Bile infusion into the renal artery and systemic circulation resulted in increased urine flow, natriuresis and kaliuresis [41–43]. The effect has been attributed to bile acid mediated through the release of prostaglandins [33]. Indomethacin inhibited this effect. In cholangiocarcinoma bile acids are also increased. Toxicity of bilirubin has been demonstrated in the neural cells by inhibition of thymidine incorporation [44]. It enhances DNA damage [45] and also inhibits protein kinase C activity [46] which is essential for cellular function.

Since mitochondrial sequestration of bilirubin occurs when bilirubin accumulation exceeds the binding capacity of albumin at the level in the neighborhood of 20 mg/dl [47]. Hyperbilirubinemia in our patients was therefore at the supraphysiologic level. Natriuresis could in fact reflect early tubular injury of the ascending limb of Henle's loop leading to concentration and dilution defect. Besides hypovolemia and renal vasodilatation, the decrease in creatinine clearance could indicate the early development of renal insufficiency, possibly due to tubuloglomerular feedback and decreased glomerular ultrafiltration coefficient. Yet, the functional changes were reversible when

jaundice subsided. This high concentration of serum bilirubin could be the critical level that marks the transition between physiologic and pathologic renal response at which tubular necrosis may occur when there is superimposing insult. In this respect the low serum albumin allowing more mitochondrial sequestration of bilirubin would be critical for the development of tubular damage and impaired renal function.

From the data presented it appears that hyperbilirubinemia is rather well tolerated by the human kidney. Impaired renal function occurs only when hypoalbuminemia exists, suggesting parenchymal hepatic damage, malnutrition or both. At this stage the patient who is salt losing becomes salt retaining. During natriuresis inadequate salt and water replacement may result in sodium depletion and volume depletion. Although blood volume has been found to be normal by some investigators [48, 49], significant hypovolemia has also been shown [50, 51]. The difference in findings could reflect the difference in state of salt and water of the subject studied. Hypoproteinemia may further contribute to the development of hypovolemia. Hypotension in severe jaundice is therefore attributed to both hypovolemia and vasodilatation. In this connection, the patients with hyperbilirubinemia are therefore susceptible to develop renal failure. Combination of hypovolemia, hypotension, increased norepinephrine sensitivity [52], renin-angiotensin activation [25], endotoxemia [53, 54] and perhaps direct tubular injury, especially in the presence of hypoproteinemia, could lead to a decrease in renal blood flow in enough degree to cause renal failure. Uricosuric effect of obstructive jaundice may also compromise renal function [55, 56], especially in the phase of decreased urine flow and acid urine. Based on the results of this study, surgical correction of biliary obstruction is very important and should be performed to prevent renal complications. Plasmapheresis may be of value when surgical treatment cannot be undertaken. Adequate salts and water replacement must be instituted to avoid volume contraction. Correction of hypoproteinemia may decrease hyperbilirubinemia-associated renal injury [47].

Acknowledgment

This work was supported by a grant from Chongkolnee Foundation. Mrs. Chomchaey Witithladda typed the manuscript.

Reprint requests to Visith Sitprija, M.D., Department of Medicine, Chulalongkorn Hospital, Rama 4 Road, Bangkok 10330, Thailand.

References

1. Dawson JL: The incidence of postoperative renal failure in obstructive jaundice. *Br J Surg* 52:663–665, 1965
2. Baum M, Sterling GA, Dawson JL: Further study into obstructive jaundice and ischaemic renal damage. *Br Med J* 2:229–231, 1969
3. Bloom D, Bomzon L, Rosendorff C, Kew MC: Renal blood flow in obstructive jaundice; An experimental study in baboons. *Clin Exp Pharmacol Physiol* 3:461–472, 1976
4. Bomzon L, Kew Mc, Rosendorff C: The effect of phenoxybenzamine and saralasin on the altered renal blood flow distribution in baboons with obstructive jaundice. *Clin Exp Pharmacol Physiol* 4:365–373, 1977
5. Hishida A, Honda N, Sudo M, Nagase M: Mechanisms of altered renal perfusion in the early stage of obstructive jaundice. *Kidney Int* 17:223–230, 1980
6. Zambraski EJ, Dunn MJ: Importance of renal prostaglandins in control of renal function after chronic ligation of the common bile duct in dogs. *J Lab Clin Med* 103:540–559, 1984
7. Alon U, Berant M, Mordechovitz D, Hashmonai M, Better OS: Effect of isolated cholaemia on systemic haemodynamics and kidney function in conscious dogs. *Clin Sci* 63:59–64, 1982
8. Finberg JPM, Syrop HA, Better OS: Blunted pressor response to angiotensin and sympathomimetic amines in bile duct ligated dogs. *Clin Sci* 61:535–539, 1981
9. Better OS, Massry SG: Effect of chronic bile duct obstruction on renal handling of salt and water. *J Clin Invest* 51:402–411, 1972
10. Bank N, Aynedjian HS: A micropuncture study of renal salt and water retention in chronic bile duct obstruction. *J Clin Invest* 55:994–1002, 1975
11. Melman A, Massry SG: Role of renal vasodilatation in the blunted natriuresis of saline infusion in dogs with chronic bile duct obstruction. *J Lab Clin Med* 89:1053–1065, 1977
12. Better OS, Aisenbrey GA, Berl T, Anderson RJ, Handelman WA, Linas SL, Guggenheim SJ, Schrier RW: Role of antidiuretic hormone in impaired urinary dilution associated with chronic bile duct ligation. *Clin Sci* 58:493–500, 1980
13. Tinsatul U, Sitprija V: Hyponatremia and hypokalemia in obstructive jaundice: A case study. *J Med Assoc Thailand* 53:437–442, 1970
14. Sitprija V: Urinary sodium excretion in jaundice, in *Proceedings of the 6th Singapore-Malaysia Congress of Medicine*, 1971, pp. 82–86
15. Chaimovitz C, Rochman J, Eidelman S, Better OS: Exaggerated natriuretic response to volume expansion in patients with primary biliary cirrhosis. *Am J Med Sci* 274:173–178, 1977
16. Sonakul D, Koompirochana C, Chinda K, Stitnimakarn T: Hepatic carcinoma with opisthorchiasis. *S Asian J Trop Med Pub Hlth* 9:215–219, 1978
17. Thorburn GD, Kopald HH, Hard JA, Hollenberg M, O'Morchoe CCC, Barger AC: Intrarenal distribution of natrient blood flow determined with Krypton 85 in the unanesthetized dogs. *Circ Res* 13:290–307, 1963
18. DiGiorgio J: Nonprotein nitrogenous constitutents, in *Clinical Chemistry: Principles and Technics*, 2nd ed, edited by Henry RJ, Cannon DC, Winkleman JW, Hagerstown, Harper and Row, 1974, pp. 503–563
19. Daugherty NA, Hammond KB, Osberg IM: Bilirubin interference with the kinetic Jaffe method for serum creatinine. *Clin Chem* 24:392–393, 1978
20. Daniel WW: *Biostatistics: A Foundation of Analysis in the Health Sciences*, 4th ed, New York, John Wiley Sons, 1987, p. 216
21. Sitprija V, Arthachinta S, Kashemsant U, Poshyachinda V: Renal blood flow study in acute renal failure. *Chula Univ Res* 2:103–119, 1975
22. Fulop M, Katz S, Lawrence C: Extreme hyperbilirubinemia. *Arch Intern Med* 127:254–258, 1971
23. Elias MM, Comin EJ, Ochoa EJ, Roderiguez-Garay EA: Evidence for a secretory component in the handling of unconjugated bilirubin by the isolated perfused rat kidney. *Can J Physiol Pharmacol* 63:1581–1585, 1985
24. Chaimovitz C, Massry SG, Friedler RM, Coburn JW: Effect of renal denervation and alpha adrenergic blockade on sodium excretion in dogs with chronic ligation of the common bile duct. *Proc Soc Exp Biol Med* 146:764–770, 1974
25. Levy M, Wexler MJ, Fechner C: Renal perfusion in dogs with experimental hepatic cirrhosis: role of prostaglandins. *Am J Physiol* 245:F521–F529, 1983
26. Cioffi WG, Demeules JE, Kahng KU, Wait RB: Renal vascular reactivity in jaundice. *Surgery* 100:356–362, 1986
27. Wait RB, Kahng KU: Renal failure complicating obstructive jaundice. *Am J Surg* 157:256–263, 1989
28. Seldin DW, Eknoyan G, Suki WN, Rector FC Jr: Localization of diuretic action from the pattern of water and electrolyte excretion. *Ann NY Acad Sci* 139:328–343, 1966
29. Dillingham MA, Better OS, Anderson RJ: Sodium taurocholate increases hydraulic conductivity in rabbit collecting tubule. *Kidney Int* 33:782–786, 1988
30. Baum M, Berry CA: Peritubular protein modulates neutral active

NaCl absorption in rabbit proximal convoluted tubule. *Am J Physiol* 248:F790–F795, 1985
31. Koyama K, Asanuma Y, Fukaya H, Omokawa S: Effect of blood purification on the kidney function of the jaundiced rat. *Artif Organs* 12:305–309, 1988
32. Caramelo C, Schrier RW: Edema of cirrhosis and its treatment, in *Regulation of Sodium and Chloride Balance*, edited by Seldin DW, Giebisch G. New York, Raven Press, 1989, pp. 353–373
33. Better OS: Nephrology Forum: Renal and cardiovascular dysfunction in liver disease. *Kidney Int* 29:598–607, 1986
34. Odell GB, Bolen JL, Poland RL, Seungdamrong S, Cukier JO: Protection from bilirubin nephropathy in jaundiced Gunn rats. *Gastroenterology* 66:1218–1224, 1974
35. Martinez-Maldonado M, Suki WN, Schenker S: Nature of urinary concentrating defect in the Gunn strain of rat. *Am J Physiol* 216:1386–1391, 1969
36. Call NB, Tischer CC: The urinary concentrating defect in the Gunn strain of rat. *J Clin Invest* 55:319–329, 1975
37. Lewis C, Mahoney P, Arias IM: Jaundice: Clinical and Pathophysiologic Features, in *Gastroenterology*, (vol. III) edited by Bockus HL, Philadelphia, W.B. Saunders Co, 1976, pp. 182–202
38. Elias MM, Comin EJ, Grosman ME, Galeazzi SA, Rodriguez Garay EA: Possible mechanism of unconjugated bilirubin toxicity on renal tissue. *Comp Biochem Physiol* 87:1003–1007, 1987
39. Ozawa K, Yamada T, Tanaka J, Ukikusa M, Tobe T: The mechanism of suppression of renal function in patients and rabbits with jaundice. *Surg Gynecol Obstet* 149:54–60, 1979
40. Better OS, Guckian V, Giebisch G, Green R: The effect of sodium taurocholate on proximal tubular reabsorption in the rat kidney. *Clin Sci* 72:139–141, 1987
41. Alon U, Berant M, Mordechovitz D, Better OS: The effect of intrarenal infusion of bile on kidney function in dog. *Clin Sci* 62:431–433, 1982
42. Topuzlu C, Stahl MW: Effect of bile infusion on the dog kidney. *N Engl J Med* 174:760–763, 1966
43. Aoyagi T, Lowenstein LM: The effect of bile acids and renal ischemia on renal function. *J Lab Clin Med* 71:686–692, 1968
44. Schiff D, Chan G, Poznansky MJ: Bilirubin toxicity in neural cell lines N 115 and NBRIOA. *Pediatr Res* 19:910–911, 1985
45. Rosenstein BS, Ducore JM: Enhancement by bilirubin of DNA damage induced in human cells exposed to photother light. *Pediatr Res* 18:3–6, 1984
46. Sano K, Nakamura H, Matsuo T: Mode of inhibitory acti of bilirubin on protein kinase C. *Pediatr Res* 19:587–590, 1985
47. Odell GB: The distribution of bilirubin between albumin and mitochondria. *J Pediatr* 68:165–180, 1966
48. Dawson JL: Acute post-operative renal failure in obstructive jaundice. *Ann R Coll Surg Engl* 42:163–181, 1968
49. Cattell WR, Birnstingl MA: Blood volume and hypotension in obstructive jaundice. *Br J Surg* 54:272–278, 1967
50. Zollinger RM, Williams RD: Surgical aspects of jaundice. *Surgery* 39:1016–1030, 1956
51. Gillet DJ: The effect of obstructive jaundice on the blood volume in rats. *J Surg Res* 11:447–449, 1971
52. Bloom D, McCalden TA, Rosendorff C: Effect of jaundice plasma on vascular sensitivity to noradrenalin. *Kidney Int* 8:149–157, 1975
53. Wardle EN, Wright NA: Endotoxin and acute renal failure associated with obstructive jaundice. *Br Med J* 4:472–473, 1970
54. Bailey ME: Endotoxin, bile salts and renal function in obstructive jaundice. *Br J Surg* 63:774–778, 1976
55. Michelis MF, Warms PC, Fusco RD, Davis BB: Hypouricemia and hyperuricosuria in Laennec cirrhosis. *Arch Intern Med* 134: 681–683, 1974
56. Tungsanga K, Boonwichit D, Lekhakula A, Sitprija V: Urine acid and urine creatinine ratio in acute renal failure. *Arch Intern Med* 144:934–937, 1984